

<https://helda.helsinki.fi>

Use of Anticholinergic Drugs According to Various Criteria and Their Association With Psychological Well-Being and Mortality in Long-Term Care Facilities

Aalto, Ulla L.

2019-09

Aalto , U L , Finne-Soveri , H , Kautiainen , H , Roitto , H-M , Öhman , H & Pitkälä , K H 2019 , ' Use of Anticholinergic Drugs According to Various Criteria and Their Association With Psychological Well-Being and Mortality in Long-Term Care Facilities ' , Journal of the American Medical Directors Association , vol. 20 , no. 9 , pp. 1156-1162 . <https://doi.org/10.1016/j.jamda.2019.02.007>

<http://hdl.handle.net/10138/318484>

<https://doi.org/10.1016/j.jamda.2019.02.007>

cc_by_nc_nd

acceptedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Use of anticholinergic drugs according to various criteria and their association with psychological well-being and mortality in long-term care facilities

Ulla L. Aalto, MD ^{a,b}; Harriet Finne-Soveri, MD, PhD ^{b,c}; Hannu Kautiainen, PhD ^d; Hanna-Maria Roitto, MD ^{a,b}; Hannareeta Öhman, MD, PhD ^{a,b}; Kaisu H Pitkälä, MD, PhD ^{a,d}

^a Department of General Practice, University of Helsinki, Helsinki, Finland; ^b Department of Social Services and Health Care, Helsinki Hospital, Helsinki, Finland; ^c National Institute for Health and Welfare, Helsinki, Finland; ^d Helsinki University Hospital, Unit of Primary Health Care, Helsinki, Finland

25 **Abstract**

26 **Objectives** 1) To compare three internationally established criteria for drugs with anticholinergic
27 properties (DAPs) and their associated factors in long-term care facilities. 2) To investigate the
28 association between use of DAPs and psychological well-being (PWB) or mortality.

29 **Design** Cross-sectional study and 1-year follow-up of all-cause mortality.

30 **Setting and Participants** Of all 4449 residents living in long-term care facilities in Helsinki in
31 2011, 2432 (≥ 65 years of age) participated after exclusion of residents with severe dementia.

32 **Measurements** Data on demographics, medication use, and active diagnoses were collected by
33 trained staff using structured questionnaires. DAP use was defined by the following three
34 international criteria: Chew's list, the Anticholinergic Risk Scale (ARS), and the Anticholinergic
35 Drug Scale (ADS). The total number of DAPs was counted and referred to as anticholinergic
36 burden. PWB was assessed by a questionnaire and yielded a score ranging from 0 to 1. Mortality
37 data was retrieved from central registers.

38 **Results** Of all participants, 85% were DAP users according to at least one of the three criteria used.
39 Overlap between the three criteria was only moderate. DAP users were younger and a larger
40 proportion of them had better cognition. However, they suffered more often from depression and
41 other psychiatric diagnoses than nonusers. DAP users had lower PWB scores than those not using
42 DAPs, and PWB decreased linearly in the overlapping groups from nonusers to those using DAPs
43 according to all three criteria. The total number of DAPs used predicted mortality.

44 **Conclusions and Implications** DAP use and PWB appear to be negatively associated. When
45 combining several criteria of DAPs, their burden predicted mortality. Clinicians should carefully
46 consider the potential benefits and harms when prescribing DAPs to older persons.

47

48 **Introduction**

49 Drugs with anticholinergic properties (DAPs) are a heterogenous group of medicines. They are
50 considered as potentially harmful to older people because of their adverse effects peripherally and
51 especially on the nervous system.¹ Some important peripheral effects of DAPs include dryness of
52 mouth, tachycardia, constipation and blurred vision.^{2,3} Undesired central side-effects of DAPs
53 include increased risk for functional decline,^{4,5} falls,⁶ cognitive decline,⁷⁻¹⁰ and increased use of
54 health services.^{11,12} Central adverse effects are known to be dose-dependent. Accordingly, a higher
55 anticholinergic burden is associated with a higher risk of adverse outcomes.⁵ DAPs are still widely
56 used among frail older people living in residential care.¹³⁻¹⁵ DAPs are frequently used to manage
57 various symptoms such as urinary incontinence, anxiety, and pain.¹⁶ The effect of DAPs on
58 mortality has also been investigated but most studies have not shown a clear relationship between
59 DAP use and mortality.^{6,13,17-19} However, there are a few studies showing contradictory
60 findings.^{8,20,21}

61 Residents in long-term care generally suffer from multiple chronic diseases and have deficits in
62 functioning and cognition. Management should thus aim towards symptom relief and palliative
63 care, and quality of life (QOL) should be one of the most important goals of care. Psychological
64 well-being (PWB) is a means to evaluate one dimension of QOL. To our knowledge, few studies
65 have investigated the association between DAPs and QOL. There is some evidence that residents
66 using DAPs living in long-term care facilities also have lower PWB than those not using DAPs.^{15,22}

67 Several lists classifying anticholinergic drugs and their anticholinergic properties have been
68 developed.^{4,5} We aimed to compare these DAP lists with each other. To explore outcomes of
69 DAPs, we chose the three most highly cited lists used internationally according to Web of Science
70 and Google Scholar.^{5,23-25} These three lists were created in various ways. While Chew's list is
71 based on measuring in vitro the serum anticholinergic activity of drugs commonly used by older
72 persons,²³ the Anticholinergic Drug Scale (ADS) is based on expert consensus²⁴ and the

Anticholinergic Risk Scale (ARS) on a literature review and expert opinion²⁵. Although some studies have compared some anticholinergic criteria,^{4,5,26,27} there is still no international consensus regarding which of these lists would be applicable in research or in clinical practice.

The objectives of the current study were to investigate 1) how the use of DAPs according to any of the anticholinergic lists studied (Chew's list, ADS and ARS) is associated with participant characteristics, 2) how participant DAP use according to these anticholinergic lists is overlapping, and 3) how participant DAP use according to these anticholinergic lists and their combinations or the total number of DAPs according to any criteria (referred to as DAP burden) are associated with self-rated health, PWB, and mortality.

Methods

This study was part of a larger study^{28,29} that investigated the nutritional status, medication use, and associated factors of older persons in all long-term care facilities in Helsinki. During October and November 2011, cross-sectional data were collected from all older persons living permanently either in assisted living facilities or in nursing homes, including group homes for persons with dementia (n=4449). Of all participants, 1097 were excluded because of patient refusal or dementia and without a close proxy to give informed consent. In addition, residents with severe dementia (score 3 on Clinical Dementia Rating (CDR) scale memory item)³⁰ (n=920) were excluded to include only those capable of responding to PWB. A total of 2432 participants thus remained in the study. Written informed consent was obtained from each participant or their closest proxy in case of significant cognitive decline (CDR 2). The study was approved by the Helsinki University Central Hospital Ethics Committee.

In each care unit, a trained nurse assessed the resident's status by retrieving background data from medical records on demographic factors and diagnoses (chronic conditions and acute illnesses) and performed the assessments and interviews according to a structured questionnaire. Each resident

97 was assessed over the course of one day. All data concerning medication use was point prevalence
98 on the same day.

99 Nutritional status was assessed by the Mini-Nutritional Assessment (MNA).³¹ Participants were
100 respectively divided into "malnourished" (<17 points), "at risk for malnutrition" (17-23.5 points),
101 and "well-nourished" (>23.5 points). Cognitive function was evaluated by the memory item of the
102 CDR scale (0-0.5, no or possible memory problems; 1, mild memory loss; 2, moderate memory
103 loss), which is a validated method to assess dementia stage.³⁰ The residents' ability to move was
104 assessed by the question "Is the resident able to move inside?" (1=yes, 2= no, needs a stick or a
105 walker, 3= no, needs another person's assistance, 4= no, unable to walk at all). Those in groups 1
106 and 2 were considered able to walk independently inside. Dependence in activities of daily living
107 (ADL) was assessed by a 4-point scale according to the CDR "personal care" item (1=fully capable
108 of self-care, 2=needs occasional prompting, 3=requires assistance in dressing, personal hygiene, and
109 keeping of personal belongings, 4=requires much help with personal care; often incontinent).³⁰
110 Those in groups 3 and 4 were considered as dependent on a caregiver's help. Participants'
111 morbidity was assessed by the Charlson Comorbidity Index (CCI).³²

112 Medication use was retrieved from medical charts during the assessment day. The resident was
113 considered a regular drug user if the medical chart indicated a regular sequence for the drug dosage.
114 Only regularly used DAPs were considered in determining the DAP burden. All medications were
115 coded according to the Anatomical Therapeutic Chemical (ATC) Classification System of the
116 World Health Organization (WHO) (WHO Collaborating Center for Drug Statistics
117 Methodology).³³ All DAPs used by the participants were listed and classified according to the
118 following three anticholinergic lists: Chew's list,²³ ADS,²⁴ and ARS²⁵. According to Chew's list,
119 22 of 107 medications studied are demonstrated to have anticholinergic activity ranging from low
120 (+) to high (+++). The ADS rates 117 drugs as anticholinergic ranging from potentially
121 anticholinergic (1) to markedly anticholinergic (3). The ARS classifies 49 drugs having

122 anticholinergic potential ranging from moderate (1) to very strong (3). The three lists consist partly
123 of different selection of anticholinergic drugs. The criteria for defining the anticholinergic potential
124 or the defined burden also differ from each other. Thus, the anticholinergic activity and the
125 anticholinergic burden is difficult to compare between the lists. In this study, the total number of
126 DAPs is referred to as DAP burden.

127 QOL was evaluated by self-rated health and PWB questionnaire. Resident's subjective health (self-
128 rated health) was evaluated by the following question: "How do you rate your current health
129 status?" (1=healthy, 2= quite healthy, 3=unhealthy, 4=very unhealthy). Those responding "healthy"
130 or "quite healthy" were considered as having good self-rated health. The PWB scale has been used
131 in several studies since 1989.³⁴⁻³⁶ It has good test-retest reliability³⁵, good prognostic validity³⁴ and
132 good concurrent validity with The World Health Organization Quality of Life – scale (WHOQOL-
133 Bref).³⁷ The residents were asked six questions as follows: 1. Are you satisfied with your life?
134 (yes/no); 2. Do you have zest for life? (yes/no); 3. Do you feel needed? (yes/no); 4. Do you have
135 plans for the future? (yes/no); 5. Do you suffer from loneliness? (seldom or never/sometimes/often
136 or always); 6. Do you feel depressed? (seldom or never/sometimes/often or always). The answers
137 were then given 0 points ("no" in questions 1-4 and "often or always" in questions 5-6), 0.5 points
138 ("sometimes" in questions 5-6) or 1 point ("yes" in questions 1-4 and "seldom or never" in
139 questions 5-6). The PWB score was then generated by adding the points together and dividing the
140 sum by the number of questions answered, thus yielding a score between 0 to 1 (0 represents the
141 poorest and 1 the best well-being).

142 We divided the participants into DAP users and nonusers according to the use of at least one DAP
143 included in one or more of the three lists mentioned above. We then generated a Venn diagram
144 creating three overlapping groups of DAP lists as mentioned above (Figure 1). Only 14 drugs were
145 considered as DAPs according to all three criteria. The number of DAPs used regularly by any
146 criteria by each participant was counted.

147 Mortality was retrieved from central registers over a 1-year follow -up.

148 **Statistical analyses**

149 Data are presented as absolute numbers, percentages for categorical variables and as means with
150 standard deviations or ranges for continuous variables. The DAP users of according to any criteria
151 were compared with nonusers with X^2 -test for categorical variables and t-test or permutation test for
152 continuous variables.

153 The relationship between DAPs and mortality or PWB was analyzed using linear regression
154 analysis and logistic models. Models included gender, age and Charlson index as covariates.

155 Shapiro-Wilk statistics were used to test the normality of variables. Stata 15.0, StataCorp LP
156 (College Station, TX, USA) statistical package was used for the analysis.

157 **Results**

158 The Venn diagram (Figure 2) illustrates the DAP users' position in the various overlapping groups
159 according to Chew's list, ADS and ARS. Of all participants, 2079 (85%) used at least one DAP
160 according to any of the three criteria; 353 (15%) did not use DAPs at all. Of DAP users, 1243
161 (60%) used at least one DAP according to ARS, 1334 (64%) used at least one DAP according to
162 Chew's list, and 1652 (79%) were administered at least one DAP according to ADS. Furthermore,
163 of DAP users, 700 (34%) used one or more DAPs according to only one list, 1379 (66%) used
164 DAPs according to at least two lists, and 771 (37%) used one or more DAPs according to all three
165 lists.

166 Compared with nonusers, DAP users were younger and had better cognition, but more often
167 suffered from depression, other psychiatric disorders, and Parkinson disease. The CCI of DAP
168 users was significantly higher than the respective value of nonusers (2.4 vs. 2.1, $p<0.001$). Those
169 using DAPs were more often at risk for malnutrition than nonusers ($p=0.049$). The mean number of

170 regularly used drugs was significantly higher among DAP users than nonusers (9.3 vs. 5.4, p
171 <0.001). While DAP users suffered more often from dry mouth than nonusers (p=0.011), no
172 difference between the groups was observed regarding constipation, diarrhea, or vomiting. No
173 significant differences existed between the groups with respect to sex distribution, education,
174 dependency on another person's help, or ability to walk inside (Table 1).

175 A larger proportion of participants not using DAPs considered their self-rated health as good
176 compared to those using DAPs (70% vs. 64%, p=0.039). Those not using DAPs also had a
177 significantly higher PWB score than those using DAPs (0.77 vs. 0.68, p<0.001). There was no
178 difference in mortality between users and nonusers (18% vs. 20%, p=0.44) (Table 1).

179 In a further analysis regarding the relationship between DAP use and psychological well-being and
180 mortality, the groups were compared to each other according to one, two, or three criteria of DAP
181 use. Using DAPs according only to one criteria did not seem to affect PWB compared to nonusers,
182 except for those using DAPs defined only by Chew's list, whose PWB was significantly lower than
183 the PWB of nonusers. When using DAPs defined by two or three criteria, the participants did have
184 significantly lower PWB compared to nonusers (p<0.001, adjusted for sex, age and comorbidity).
185 There was no significant difference in mortality between the overlapping groups (p=0.41, adjusted
186 for sex, age, and comorbidity) (Figure 3). We further adjusted for number of medications, and the
187 findings were essentially the same (data not shown).

188 When exploring the total burden of DAPs (i.e. the total number of DAPs according to any of the
189 three criteria used), PWB decreased as a linear trend as the number of DAPs increased (p<0.001 for
190 linearity, adjusted for sex, age, and comorbidity). The risk of mortality increased along with
191 increasing number DAPs used (p=0.006 for linearity, adjusted for age, sex, and comorbidity)
192 (Figure 4). We further adjusted for number of medications, and the findings were essentially the
193 same (data not shown).

194 We further performed sensitivity analyses by excluding all those with depression diagnosis. All the
195 findings were essentially the same (data not shown).

196 **Discussion**

197 Our study revealed that DAP use seems to have an inverse association with the PWB of older
198 people living in long-term care facilities. Even though the DAP users were younger and had fewer
199 cognitive problems than nonusers, their self-rated health and PWB was poorer than that of nonusers.
200 DAP users suffered more often from depression and other psychiatric illnesses and had more
201 comorbidities than nonusers. PWB decreased linearly as the number of DAPs increased. By
202 investigating the overlapping of various criteria of DAPs among DAP users, we observed that
203 neither the criteria alone nor a combination of two or three criteria predicted mortality. Instead, the
204 total number of DAPs used according to any of these criteria (i.e. the total anticholinergic burden)
205 was associated with increased risk of mortality.

206 Our study has several strengths and limitations. One strength of the study is the relatively large
207 sample of older, frail people living in long-term care facilities in Helsinki. The data were collected
208 by trained nurses by the same procedure in every participating unit. The information on
209 demographic data, medication use and medical diagnoses were retrieved from each participant's
210 medical records. The mortality data were retrieved from central registers, which is 100% complete
211 in Finland. The PWB scale is a well-validated tool even among older people with cognitive decline.
212 Another strength was the use of three internationally well-known criteria in defining DAPs.
213 Furthermore, we also focused on the burden of DAPs of each participant by counting the total
214 number of DAPs according to any of the three lists.

215 One limitation of our study is its cross-sectional nature. Thus, it is not possible to draw definite
216 conclusions between DAP use and PWB or mortality. The total time exposure of each individual
217 medication is not known, as the data were collected as a point prevalence over one day and the

218 follow-up time was one year. The original indication of the drugs is also unknown. Only regularly
219 administered drugs were calculated in the total anticholinergic load, not drugs given *pro re nata*.
220 All drugs were administered by nurses and adherence should thus be nearly 100%. We also were
221 unable to use the burden defined by the various scales as the three scales are not congruent in
222 defining the anticholinergic burden; this can be considered a limitation. Our study demonstrates
223 how relative the definitions and burden are according to various DAP scales. There may be
224 confounding by indication bias regarding the use of DAPs and PWB. It is possible that PWB was
225 poorer because of DAP use, or because the participants were given DAPs to manage some
226 underlying disease (e.g. depression) that might have lowered their PWB score. However, our
227 sensitivity analyses showed that the results were the same when those with depression were
228 excluded. The results are consistent with our previous study from the same study population¹⁵ in
229 which we observed that possible underlying depression did not explain the poorer PWB among
230 DAP users.

231 DAP users were younger as in previous studies.^{38,39} DAP users suffered less often from cognitive
232 problems compared to nonusers. In contrast to our previous study¹⁵, in the current study DAP users
233 had more comorbidities according to the CCI than nonusers. One possible explanation is that the
234 ADS contains a large number of very common drugs for coronary and heart diseases.

235 Our study demonstrates how the three scales differ from each other. Our combined list from three
236 scales includes 138 DAPs but only 14 drugs are common in all scales. Of these 14 drugs, the most
237 commonly used drugs were olanzapine and clozapine. The ADS scale has a high number of DAPs
238 that are not included in other lists. Chew's list is quite compact but contains drugs frequently used
239 by older people (e.g. mirtazapine and citalopram). Consistent with previous studies comparing
240 various DAP scales, the scales seem to predict different outcomes from each other.^{12,40} However, to
241 our knowledge there are no prior studies exploring how DAP use overlaps in real-life settings or
242 how the number of DAPs used according to the three scales impacts on important outcomes.

243 When comparing overlapping groups, we did not observe any significant differences in all-cause
244 mortality between the groups, even after adjusting for age, sex, and CCI. This can be explained by
245 the fact that the anticholinergic burden does not necessarily increase even though DAP use is
246 defined by multiple criteria. Instead, when considering the total number of DAPs defined by any of
247 the three criteria, an association with increased mortality was demonstrated even after adjusting for
248 age, sex, and CCI. This is a new finding compared to most prior studies.^{6,13,17-19} Only one prior
249 scale, the Anticholinergic Cognitive Burden Scale (ACB)⁴¹, has shown in several studies predictive
250 value on mortality.^{6,8,19,21} The ACB scale includes 88 DAPs, thus emphasizing that higher number
251 of potential DAPs may have impact on mortality. There was a linear relationship between mortality
252 and higher number of these drugs used.

253 To our knowledge, despite the importance of PWB of older persons living their last years in long-
254 term care facilities, there is still a lack of studies investigating the relationship between DAP use
255 and PWB. While Kolanowski et al.⁴² found no association between anticholinergic burden and
256 engagement in activity (an indicator of QOL in persons with dementia), Teramura-Grönblad et al.²²
257 and Aalto et al.¹⁵ found an association between PWB and DAP use. In an Australian study
258 assessing older people living in residential care facilities, an association was found between the use
259 of potentially harmful medicines defined by the Drug Burden Index and the self-reported QOL
260 measured with the Quality of Life-Alzheimer's disease questionnaire.⁴³ A small American study
261 among community-dwelling older adults with dementia also revealed an association between DAP
262 use and lower health-related QOL.⁴⁴ Our current study supports the earlier findings of the
263 association between DAPs and poorer PWB.

264 **Conclusions and Implications**

265 The use of DAPs seems to have a negative association with PWB of older and vulnerable people
266 living in institutionalized care. The DAP burden was linearly associated with poorer PWB. Neither
267 a single criterium alone nor a combination of two or three criteria predicted mortality. Instead, we

268 found a weak, linear association between the total number of DAPs and increased mortality. The
269 most appropriate criteria for DAPs in assessing the anticholinergic load of older people remains
270 thus far unknown and further studies are needed.

271
272 The authors declare no conflicts of interest directly relevant to this report.

273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296

297 Table 1. Participants' characteristics according to usage of drugs with anticholinergic properties (DAPs).

	Using no DAPs n=353 (15%)	Using one or more DAPs n=2079 (85%)	p-value ¹
Female, n (%)	254 (72)	1568 (75)	0.16
Age, mean (SD ²)	86 (7)	84 (8)	<0.001
Education <8 yrs, n (%)	201 (57)	1144 (55)	0.50
Depression, n (%)	37 (10)	489 (24)	<0.001
Other psychiatric diagnosis, n (%)	18 (5)	291 (14)	<0.001
Parkinson disease, n (%)	9 (3)	138 (7)	0.003
CCI ³ , mean (SD ²)	2.1 (1.4)	2.4 (1.5)	<0.001
MNA ⁴ , n (%)			0.049
At risk for malnutrition (17-23.5 points), n (%)	206 (59)	1353 (65)	
Moderate cognitive decline (CDR 2) ⁵ , n (%)	154 (44)	679 (33)	<0.001
Dependent for personal care (CDR personal care class 2-3) ⁶ , n (%)	285 (81)	1724 (83)	0.32
Ability to walk inside, n (%)	117 (50)	1115 (54)	0.22
Number of drugs used regularly, mean (SD ²)	5.4 (2.9)	9.3 (3.4)	<0.001
Dry mouth, n (%)	36 (10)	319 (15)	0.011
Constipation, n (%)	125 (35)	719 (35)	0.76
Diarrhea, n (%)	32 (9)	253 (12)	0.094
Vomiting, n (%)	12 (3)	97 (5)	0.29
Self-rated health good, n (%)	246 (70)	1331 (64)	0.039
PWB ⁷ , mean (SD ²)	0.77 (0.23)	0.68 (0.26)	<0.001
One-year mortality, n (%)	71 (20)	374 (18)	0.44

298

299

¹ p-value, adjusted for age, sex, comorbidity, CDR and dependency for personal care

² SD= standard deviation

³ CCI= Charlson Comorbidity Index (Charlson et al. 1987)³²

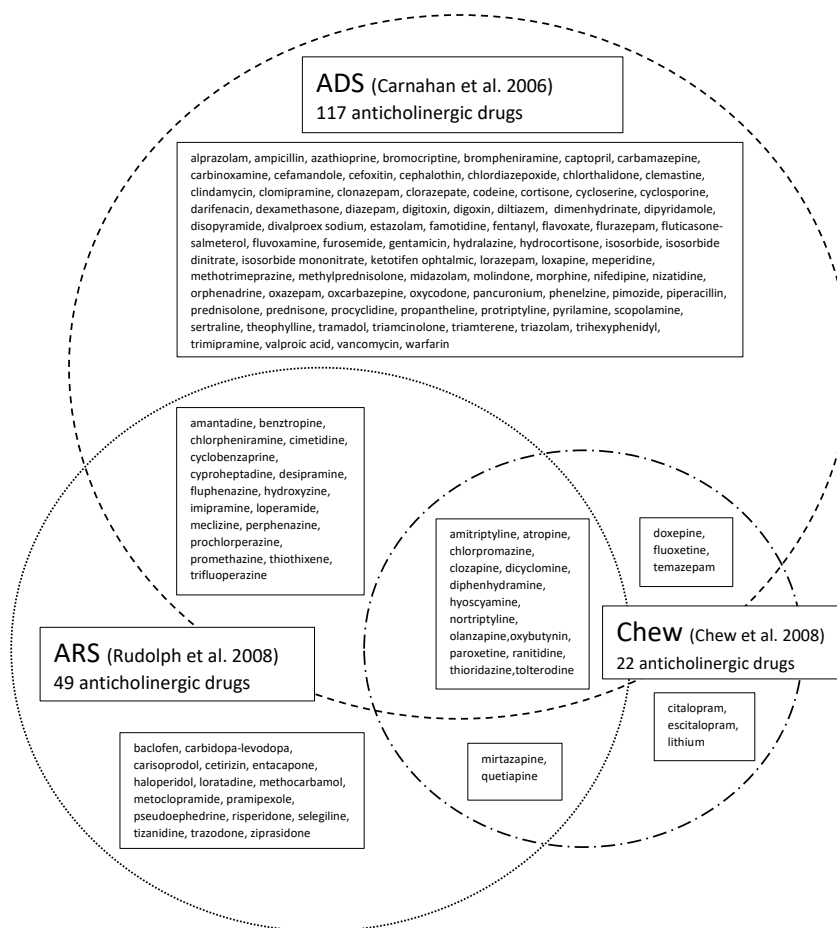
⁴ MNA= Mini-Nutritional Assessment (Vellas et al. 1999)³¹

⁵ CDR=Clinical Dementia Rating, "memory" item (Hughes et al. 1982)³⁰

⁶ CDR, "personal care" item (Hughes et al. 1982)³⁰

⁷ PWB= psychological well-being (Routasalo et al. 2009)³⁶

Figure 1.



316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336

Venn Diagram
N=2432

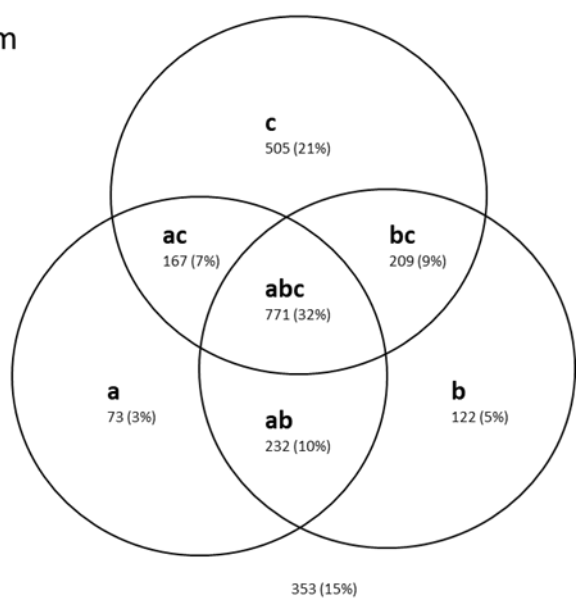
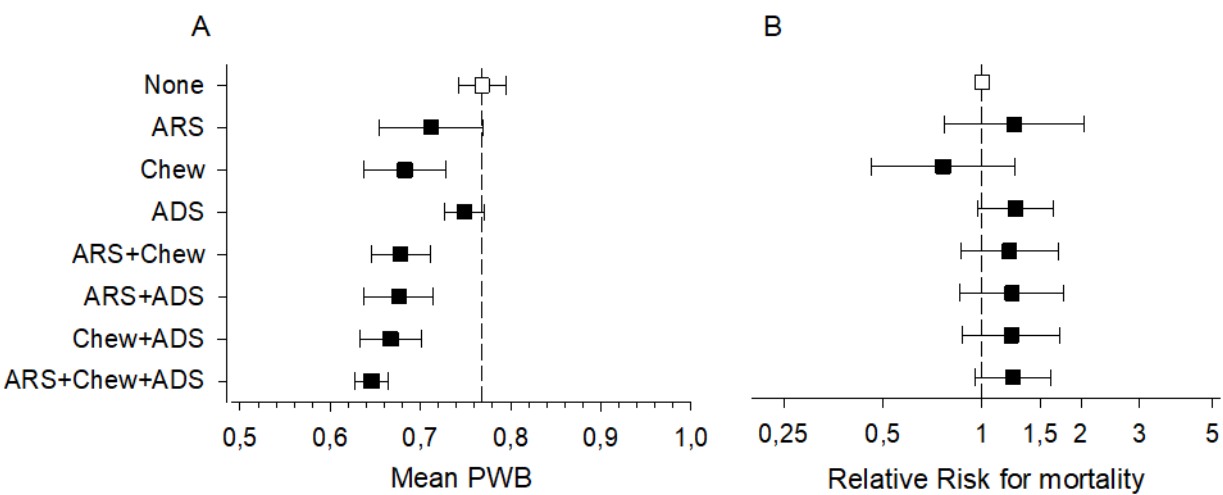


Figure 2.

337



338

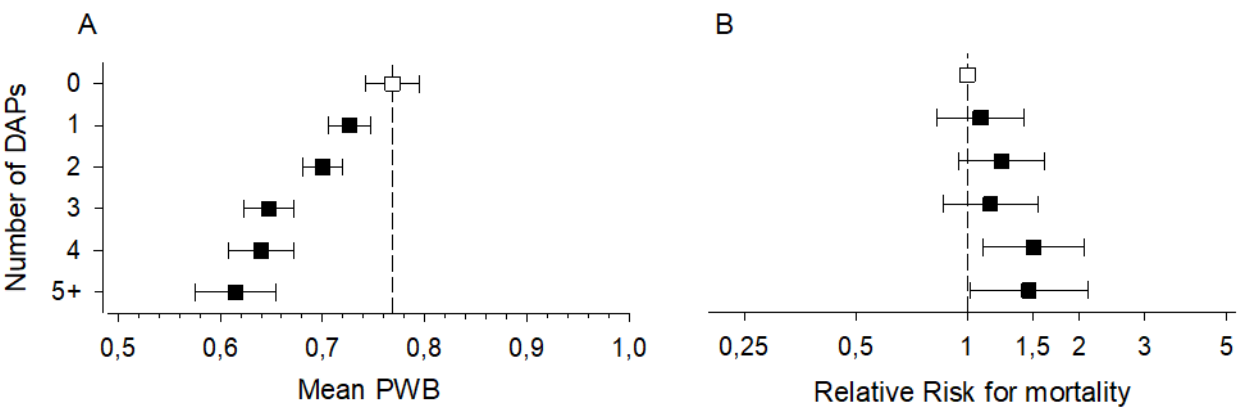
339 Figure 3.

340

341

342

343



344

345 Figure 4.

346

347

348

349

350

351

352

353

354 **Legends to figures**

355 Figure 1.

356 Venn diagram showing how the three scales on drugs with anticholinergic properties (DAP)
357 overlap. Anticholinergic Risk Scale (ARS)²⁵, Anticholinergic Drug Scale (ADS)²⁴ and Chew's list²³

358

359 Figure 2.

360 Venn diagram showing how the participants fell into groups using drugs with anticholinergic
361 properties (DAP) in the overlapping groups of three DAP scales. DAP users N=2079 (85%), non-
362 users N=353 (15%)

363 DAP users by: a=Anticholinergic Risk Scale (ARS);²⁵ b=Chew's list (Chew);²³ c=Anticholinergic
364 Drug Scale (ADS);²⁴ ab=ARS+Chew; ac=ARS+ADS; bc=Chew+ADS; abc=ARS+Chew+ADS.

365

366 Figure 3.

367 A, Psychological well-being (PWB) in groups according to use of drugs with anticholinergic
368 properties (DAP) by various criteria and how the overlapping groups predicted PWB (p<0.001).

369 None=not using any DAP; Anticholinergic Risk Scale (ARS)²⁵; Chew's list (Chew)²³;
370 Anticholinergic Drug Scale (ADS)²⁴

371 B, Relative risk for mortality is presented in respective groups (p=0.41).

372 The relationships between DAPs and PWB or mortality were analyzed using linear regression
373 analysis (mean) and logistic models (relative risk). Models included sex, age, and Charlson
374 comorbidity index as covariates.

375

376 Figure 4.

377 A, Psychological well-being (PWB) in groups using no drugs with anticholinergic properties
378 (DAPs) or using 1 to 5 or more DAPs. The higher the number of DAPs the lower is PWB (p<0.001
379 for linearity).

380 B, Relative risk for mortality is presented in respective groups. The number of DAPs has a linear
381 relationship with mortality (p=0.006 for linearity).

382 The relationships between number of DAPs and PWB or mortality were analyzed using linear
383 regression analysis (mean) and logistic models (relative risk). Models included sex, age, and
384 Charlson comorbidity index as covariates.

385

386

387

388

389

390 **References**

- 391 1. Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry*. 2001;62
392 Suppl 21:11-14.
- 393 2. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. *J R Soc Med*
394 2000;93:457-462
- 395 3. Chapter 13 Cholinergic transmission. In: Rang HP, Ritter JM, Flower RJ, Henderson G, editors.
396 Rang and Dale's Pharmacology. 8th ed. Churchill Livingstone: Elsevier; 2016.
- 397 4. Villalba-Moreno AM, Alfaro-Lara ER, Pérez-Guerrero MC, et al. Systematic review on the use
398 of anticholinergic scales in poly pathological patients. *Arch Gerontol Geriatr* 2016;62:1-8.
- 399 5. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic
400 risk scales and adverse outcomes in older people: A systematic review. *BMC Geriatr* 2015;15:31.
- 401 6. Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive
402 impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. *Br*
403 *J Clin Pharmacol* 2015;80:209-220.
- 404 7. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: A clinical
405 review. *Clin Interv Aging* 2009;4:225-233.
- 406 8. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive
407 impairment in the older population: The medical research council cognitive function and ageing
408 study. *J Am Geriatr Soc* 2011;59:1477-1483.
- 409 9. Gerretsen P, Pollock BG. Cognitive risks of anticholinergics in the elderly. *Aging Health*.
410 2013;9:159-166.
- 411 10. Uusvaara J, Pitkala KH, Kautiainen H, et al. Detailed cognitive function and use of drugs with
412 anticholinergic properties in older people: A community-based cross-sectional study. *Drugs Aging*
413 2013;30:177-182.

- 414 11. Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and
415 associations with adverse health outcomes in older people. *J Am Geriatr Soc* 2015;63:85-90.
- 416 12. Hsu WH, Wen YW, Chen LK, Hsiao FY. Comparative associations between measures of anti-
417 cholinergic burden and adverse clinical outcomes. *Ann Fam Med* 2017;15(6):561-569.
- 418 13. Kumpula EK, Bell JS, Soini H, Pitkälä KH. Anticholinergic drug use and mortality among
419 residents of long-term care facilities: A prospective cohort study. *J Clin Pharmacol* 2011;51:256-
420 263.
- 421 14. Palmer JB, Albrecht JS, Park Y, et al. Use of drugs with anticholinergic properties among
422 nursing home residents with dementia: A national analysis of medicare beneficiaries from 2007 to
423 2008. *Drugs Aging* 2015;32:79-86.
- 424 15. Aalto UL, Roitto HM, Finne-Soveri H, et al. Use of anticholinergic drugs and its relationship
425 with psychological well-being and mortality in long-term care facilities in Helsinki. *J Am Med Dir*
426 *Assoc* 2018;19:511-515.
- 427 16. Dauphinot V, Mouchoux C, Veillard S, et al. Anticholinergic drugs and functional, cognitive
428 impairment and behavioral disturbances in patients from a memory clinic with subjective cognitive
429 decline or neurocognitive disorders. *Alzheimers Res Ther* 2017;9:58.
- 430 17. Luukkanen MJ, Uusvaara J, Laurila JV, et al. Anticholinergic drugs and their effects on
431 delirium and mortality in the elderly. *Dement Geriatr Cogn Dis Extra* 2011;1:43-50.
- 432 18. Wilson NM, Hilmer SN, March LM, et al. Associations between drug burden index and
433 mortality in older people in residential aged care facilities. *Drugs Aging* 2012;29:157-165.
- 434 19. Fox C, Smith T, Maidment I, et al. Effect of medications with anti-cholinergic properties on
435 cognitive function, delirium, physical function and mortality: A systematic review. *Age Ageing*
436 2014;43:604-615.

- 437 20. Gutiérrez-Valencia M, Martínez-Velilla N, Vetrano DL, et al. Anticholinergic burden and health
438 outcomes among older adults discharged from hospital: results from the CRIME study. *Eur J Clin*
439 *Pharmacol* 2017;73:1467-1474.
- 440 21. Myint PK, Fox C, Kwok CS, et al. Total anticholinergic burden and risk of mortality and
441 cardiovascular disease over 10 years in 21,636 middle-aged and older men and women of EPIC-
442 Norfolk prospective population study. *Age Ageing* 2015;44:219-225.
- 443 22. Teramura-Grönblad M, Muurinen S, Soini H, et al. Use of anticholinergic drugs and
444 cholinesterase inhibitors and their association with psychological well-being among frail older
445 adults in residential care facilities. *Ann Pharmacother* 2011;45:596-602.
- 446 23. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications
447 commonly used by older adults. *J Am Geriatr Soc* 2008;56:1333-1341.
- 448 24. Carnahan RM, Lund BC, Perry PJ, et al. The anticholinergic drug scale as a measure of drug-
449 related anticholinergic burden: Associations with serum anticholinergic activity. *J Clin Pharmacol*
450 2006;46:1481-1486.
- 451 25. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and
452 anticholinergic adverse effects in older persons. *Arch Intern Med* 2008;168:508-513.
- 453 26. Duran CE, Azerman M, Vander Stichele RH. Systematic review of anticholinergic risk scales in
454 older adults. *Eur J Clin Pharmacol* 2013;69:1485-1496.
- 455 27. Naples JG, Marcum ZA, Perera S, et al. Concordance between anticholinergic burden scales. *J*
456 *Am Geriatr Soc* 2015;63:2120-2124.
- 457 28. Suominen M, Muurinen S, Routasalo P, et al. Malnutrition and associated factors among aged
458 residents in all nursing homes in helsinki. *Eur J Clin Nutr* 2005;59:578-583.
- 459 29. Suominen MH, Sandelin E, Soini H, Pitkala KH. How well do nurses recognize malnutrition in
460 elderly patients? *Eur J Clin Nutr* 2009;63:292-296.

- 461 30. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. Br J
462 Psychiatry. 1982;140:566-572.
- 463 31. Vellas B, Guigoz Y, Garry PJ, et al. The mini nutritional assessment (MNA) and its use in
464 grading the nutritional state of elderly patients. Nutrition. 1999;15:116-122.
- 465 32. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic
466 comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;40:373-383.
- 467 33. WHO Collaborating Centre for Drug Statistics Methodology. The Anatomical Therapeutical
468 Chemical Classification System. Norwegian Institute of Public Health. Available at:
469 https://www.whocc.no/atc_ddd_index/. Accessed September 20, 2010.
- 470 34. Pitkala KH, Laakkonen ML, Strandberg TE, Tilvis RS. Positive life orientation as a predictor of
471 10-year outcome in an aged population. J Clin Epidemiol 2004;57:409-414.
- 472 35. Savikko N, Routasalo P, Tilvis RS, et al. Loss of parents in childhood - associations with
473 depression, loneliness, and attitudes towards life in older finnish people. Int J Older People Nurs
474 2006;1:17-24.
- 475 36. Routasalo PE, Tilvis RS, Kautiainen H, Pitkala KH. Effects of psychosocial group
476 rehabilitation on social functioning, loneliness and well-being of lonely, older people: randomized
477 controlled trial. J Adv Nurs 2009;65:297-305.
- 478 37. Huusko T, Kautiainen H, Pitkala H. WHOQOL-Bref and 150 in measuring quality-of-life
479 among older caregivers. In: Huusko T, Strandberg T, Pitkala K, editors. Can Older People's
480 Quality of Life Be Measured? [Finnish]. Helsinki, Finland: The Central Union for the Welfare of
481 the Aged; 2006. p. 76-90.
- 482 38. Chatterjee S, Mehta S, Sherer JT, Aparasu RR. Prevalence and predictors of anticholinergic
483 medication use in elderly nursing home residents with dementia: Analysis of data from the 2004
484 national nursing home survey. Drugs Aging 2010;27:987-997.

- 485 39. Landi F, Dell'Aquila G, Collamati A, et al. Anticholinergic drug use and negative outcomes
486 among the frail elderly population living in a nursing home. *J Am Med Dir Assoc* 2014;15:825-829.
- 487 40. Lertxundi U, Domingo-Echaburu S, Hernandez R, et al. Expert-based drug lists to measure
488 anticholinergic burden: similar names, different results. *Psychogeriatrics* 2013;13:17-24.
- 489 41. Boustani M, Campbell N, Munger S, et al. Impact of anticholinergics on the aging brain: a
490 review and practical application. *Aging Health* 2008;4:311-320.
- 491 42. Kolanowski A, Fick DM, Campbell J, et al. A preliminary study of anticholinergic burden and
492 relationship to a quality of life indicator, engagement in activities, in nursing home residents with
493 dementia. *J Am Med Dir Assoc* 2009;10:252-257.
- 494 43. Bosboom PR, Alfonso H, Almeida OP, Beer C. Use of potentially harmful medications and
495 health-related quality of life among people with dementia living in residential aged care
496 facilities. *Dement Geriatr Cogn Dis Extra* 2012;2:361-371.
- 497 44. Sura SD, Carnahan RM, Chen H, Aparasu RR. Anticholinergic drugs and health-related quality
498 of life in older adults with dementia. *J Am Pharm Assoc (2003)* 2015;55:282-287.

499

500

501